

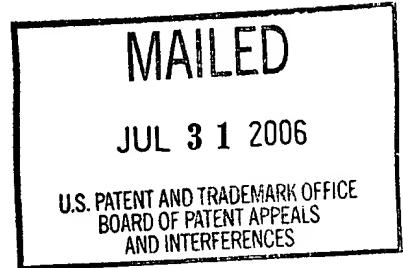
The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte KIRK HOGAN

Appeal No. 2006-1517
Application No. 09/976,423



ON BRIEF

Before BARRY, ADAMS, and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to kits for determining risk of surgery- or anesthesia-related complications. The examiner has rejected the claims as based on new matter, anticipated, and obvious in view of the prior art. We have jurisdiction under 35 U.S.C. § 134. We reverse all of the rejections.

Background

"Although surgery saves many lives, surgical complications result in many instances of mortality and morbidity. Complications related to surgery and anesthesia include infections, excessive blood loss, thrombosis, nausea and vomiting, and anesthesia reactions." Specification, page 1.

Mutations in several genes have been linked to increased risk of surgery- and anesthesia-related complications including malignant hyperthermia, sepsis, and possible toxicity of anesthetics and other drugs. See page 2, lines 3-4 and 22-24; page 2, line 27 to page 3, line 2; and page 3, lines 12-13.

The specification discloses “a kit for generating a perioperative genomic profile for a subject, comprising a reagent capable of detecting the presence of a variant allele of two or more genes markers [sic] selected from [particular genes]; and instructions for using the kit for generating the perioperative genomic profile for the subject.” Page 6, lines 15-20.

“In some embodiments, a computer-based analysis program is used to translate the raw data generated by the genomic profile (e.g., the presence or absence of a given SNP [single nucleotide polymorphism; page 28, line 19] or mutation) into data of predictive value for the clinician (e.g., probability of abnormal pharmacological response, presence of underlying disease, or differential diagnosis of known disease). . . . Thus, . . . the clinician, who is not likely to be trained in genetics or molecular biology, need not understand the raw data of the genomic profile. The data is presented directly to the clinician in its most useful form.” Page 50, lines 8-17.

“For example, in some embodiments . . . , a sample is obtained from a subject and submitted to a genomic profiling service (e.g., clinical lab at a medical facility, genomic profiling business, etc.) to generate raw data. . . . Once received by the genomic profiling service, the sample is processed and a genomic profile is produced (i.e., genomic data), specific for the medical or surgical procedure the subject will undergo. The genomic profile data is then prepared in a format suitable for

interpretation by a treating clinician. For example, rather than providing raw sequence data, the prepared format may represent a risk assessment for various treatment options." Page 50, line 22, to page 51, line 10.

Discussion

1. Claim construction

Claims 72-107 are pending and on appeal. Claims 72 and 106 are representative and read as follows:

72. A kit for generating a perioperative genomic profile for a subject, comprising:

- a) reagents configured such that when exposed to a sample containing target nucleic acid from a perioperative subject, said subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure, are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the group consisting of BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF α and TNF β so as to generate a genomic profile for use in selecting a perioperative course of action for said subject; and
- b) a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents.

106. A perioperative genomic profile kit having component parts configured such that when exposed to a sample containing target nucleic acid from a perioperative subject, said subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure, are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the group consisting of BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRRR, CBS, TNF α and TNF β , so as to generate a genomic profile for use in selecting a perioperative course of action for said subject and thereby providing a subject-specific clinical pathway for said subject, comprising information to optimize perioperative care that, based at least on the presence or absence of said variant alleles of two or more genes associated with two or more conditions selected from the group consisting of BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF α and TNF β measured by said kit, directs a user to a specific clinical pathway of medical intervention for said subject.

Thus, claim 72 is directed to a kit comprising “reagents” and “a computer program.” The claim specifies that the reagents in the kit are “configured such that when exposed to a sample containing target nucleic acid from a perioperative subject, . . . [they] are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from [a group of specific genes].”

As we interpret the claim language, it requires reagents that are sufficient to detect the presence or absence of variant alleles in at least two of the recited genes when exposed to a sample containing a target nucleic acid. That is, the reagents in the kit can be combined with a sample from a perioperative subject and processed to detect the presence of variant alleles in the specified genes, without the addition of other reagents. This interpretation is required by the claim language: if reagents not included in the kit were required to detect the presence of variant alleles in the recited genes, then the kit would not comprise reagents “sufficient to detect” those alleles.

The other passages in part (a) of claim 72 do not constitute limitations of the claimed kit. The passage stating that the “subject [is] a patient scheduled for a surgical procedure that has not yet completed said surgical procedure” recites nothing more than an intended use of the claimed kit. That is, the specification states that the kit is intended to be used shortly before or during surgery (see page 9, lines 3-11) but that intended use does not limit the components of a kit: the same components would be required to detect the presence of the recited alleles regardless of whether the kit was used perioperatively.

In addition, the passage stating that the reagents “generate a genomic profile for use in selecting a perioperative course of action for said subject,” merely recites the intended outcome of using the regents. The specification defines “genomic profile” as “a set of information about a given ‘subject’s’ genes (e.g., the presence or absence of a specific set of mutations or ‘SNPs’).” Page 27, lines 13-14. Thus, the “genomic profile” recited in the claims refers simply to the data showing the presence or absence of the recited variant alleles, and reagents that are sufficient to detect alleles in at least two of the recited genes are therefore, by definition, capable of generating a genomic profile.

Finally, the kit defined by claim 72 comprises “a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents.”

Claim 106 is similar to claim 72 in that it requires the same reagents (which are termed “component parts” in claim 106). As with claim 72, the claim language stating that the “subject [is] a patient scheduled for a surgical procedure that has not yet completed said surgical procedure” recites nothing more than an intended use of the claimed kit, and does not further limit the claim. Likewise, the recitation “so as to generate a genomic profile” also does not further limit the claim, because detecting the presence or absence of alleles in at least two of the recited genes by definition generates a genomic profile.

Finally, the claim language following “so as to generate a genomic profile” recites nothing more than the intended use of the genomic profile that is to be generated by the kit, and does not further limit the claimed kit. That is, the kit requires regents (“component parts”) sufficient to detect polymorphisms in at least two of the recited genes, thereby generating a genomic profile, but the reagents that are capable of

detecting those alleles are the same regardless of whether the resulting genomic profile is used as recited in claim 106; the intended use language at the end of the claim therefore does not constitute a structural limitation of the claimed kit.

Claim 106 differs from claim 72 in that it does not require the claimed kit to comprise a computer program in addition to the component parts that detect the presence of variant alleles.

2. Written Description

The examiner rejected claims 72-105 under 35 U.S.C. § 112, first paragraph, for lack of adequate written description; that is, being based on new matter. The examiner argued that “the specification does not describe or discuss ‘a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents.’” Examiner’s Answer, paragraph bridging pages 3 and 4. See also page 6: “The concept of ‘a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents’ does not appear to be part of the originally filed invention.”

However, on page 4 of the Examiner’s Answer, the examiner quotes the following passage from the specification: “In some embodiments, a computer-based analysis program is used to translate the raw data generated by the genomic profile (e.g., the presence or absence of a given SNP or mutation) into data of predictive value for the clinician (e.g., probability of abnormal pharmacological response, presence of underlying disease, or differential diagnosis of known disease)” (emphases added). While this passage does not use precisely the same words as claim 72, we agree with Appellant that it reasonably describes the limitation recited in the claim.

The examiner also rejected the claims because “[t]here is no disclosure in the instant specification of a kit comprising reagents and a computer program.” Examiner’s Answer, page 4. See also page 5 (“there are no teachings of a computer program within a kit”).

Again, however, we agree with Appellants that the specification describes the combination of a computer program and allele-detecting reagents, although not precisely in the terms used in the claims. The specification describes kits comprising reagents capable of detecting variant alleles of various genes (see, e.g., page 6, lines 15-20) and describes a “computer-based analysis program . . . to translate the raw data” generated by such kits (page 50, lines 8-12).

Moreover, the specification states that “Figure 2 illustrates the transformation of a sample . . . into data useful for the clinician.” Page 50, lines 21-22. “[A] sample is obtained from a subject and submitted to a genomic profiling service (e.g., clinical lab at a medical facility, genomic profiling business, etc.) to generate raw data. . . . Once received by the genomic profiling service, the sample is processed and a genomic profile is produced (i.e., genomic data), specific for the medical or surgical procedure the subject will undergo.” Page 50, line 22 to page 51, line 7.

The specification also contemplates that the party generating the genomic profile from the sample will process the data into a more easily understood format. See page 51, lines 8-15: “The genomic profile data is then prepared in a format suitable for interpretation by a treating clinician. For example, rather than providing raw sequence data, the prepared format may represent a risk assessment for various treatment options. . . . [I]n some embodiments, the genomic profiling service generates a report

that can be printed for the clinician . . . or displayed to the clinician on a computer monitor."

In our view, these disclosures reasonably support the concept of combining reagents for detecting variant alleles with a computer program to analyze data indicating the presence or absence of such variant alleles. Adequate written description does not require literal support in the specification: "In order to satisfy the written description requirement, the disclosure as originally filed does not have to provide in haec verba support for the claimed subject matter at issue." Purdue Pharma L.P. v. Faulding, Inc., 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000). Adequate written description requires only a disclosure that conveys with reasonable clarity to those skilled in the art that the inventor was in possession of the invention. See id.

In this case, we conclude that the examiner has not adequately explained why the description provided by the specification would be considered inadequate, by those skilled in the art, to show possession of the instantly claimed kit. We therefore reverse the rejection based on the first paragraph of 35 U.S.C. § 112.

3. Anticipation

The examiner rejected claims 72-105 under 35 U.S.C. § 102(b) as anticipated by Applied Biosystems,¹ and rejected claims 106 and 107 as anticipated by Perkin Elmer.²

With regard to Applied Biosystems, the examiner reasoned that

Applied Biosystems provides several products which are packaged for distribution, kits, which allow for detecting the presence of variant alleles of two or more genes. Applied Biosystems products for sale include: a DNA analysis system; software for genetic analysis; . . . PRISM Ready reaction

¹ Sales catalog of Applied Biosystems, Inc., pp. 135-157 and 160-164 (1993)

² PCR Systems, Reagents & Consumables catalog, Perkin Elmer, pp. 15-18 (1995)

cycle sequencing kits; AmpliTaq Cycling Sequencing Kits; . . . etc. Each of these products is capable of detecting the presence of variant alleles of two or more genes. Applied Biosystems teaches numerous computer programs which are sold with the DNA analysis system, for example.

Examiner's Answer, page 7. Similarly, with respect to Perkin Elmer, the examiner reasoned that

Perkin Elmer provides several products which are packaged for distribution, kits, which allow for detecting the presence of variant alleles of two or more genes. First, Perkin Elmer teaches the GeneAmp PCR Reagent Kit with AmpliTaq DNA polymerase. . . . This kit provided by Perkin Elmer contains reagents which allow for detection of variant alleles of two or more genes.

Id., page 9.

Appellant argues that "the Examiner has ignored [certain] claim elements entirely i.e., reagents sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the specified group consisting of BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNFa and TNF β It is a matter of simple fact that the 1993 Applied Biosystems Product Catalog is insufficient, standing alone, to detect the alleles of the perioperative genomic profile kits of the present invention without more, i.e., specific reagents to do so."

Appeal Brief, page 24. See also Reply Brief, page 11 (arguing that Perkin Elmer does not teach kits comprising parts that are "sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from" the recited genes).

We agree with Appellant that neither Applied Biosystems nor Perkin Elmer disclose the kits defined by instant claims 72 and 106. As Appellant points out, the claimed kits must include reagents (or component parts) "sufficient to detect" variant

alleles in at least two of the recited genes. We agree with this interpretation of the claims.

None of the kits disclosed by either Applied Biosystems or Perkin Elmer include reagents that are specific to any of the genes recited in claims 72 and 106. The kits disclosed in the references contain reagents for performing a polymerase chain reaction (PCR) process or for carrying out DNA sequencing. Granted, the kits disclosed by the references would allow a skilled worker to amplify and sequence any given DNA fragment, given primers specific to the desired fragment. What is missing from the references, however, is a disclosure of primers specific to any of the genes recited in claims 72 and 106.

"[A]nticipation requires that all of the elements and limitations of the claim are found within a single prior art reference." Scripps Clinic & Research Found. v. Genentech, Inc., 927 F.2d 1565, 1576, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991). Applied Biosystems does not disclose a product meeting all the limitations of claim 72 and Perkin Elmer does not disclose a product meeting all the limitations of claim 106. We therefore reverse the rejections based on Applied Biosystems and Perkin Elmer.

4. Obviousness

The examiner rejected claims 106 and 107 under 35 U.S.C. § 103(a) as obvious in view of either Rosen³ and Ahern⁴ or Tarkowski⁵ and Ahern. The examiner noted that "Rosen teaches [that] genotyping of selected loci of the TNF-alpha and TNF-beta

³ Rosen, U.S. 2002/0119468 A1, published August 29, 2002

⁴ Ahern, "Biochemical, reagent kits offer scientists good return on investment," The Scientist, Vol. 9, p. 20 (1995)

⁵ Tarkowski et al., "TNF gene polymorphism and its relation to intracerebral production of TNF α and TNF β in AD," Neurology, Vol. 54, pp. 2077-2081 (2000)

coding regions was performed by PCR amplification and restriction digestion," (Examiner's Answer, page 11) and that "Tarkowski teaches analyses of TNFalpha and TNFbeta gene polymorphism[s]," using PCR and restriction enzyme digestion. Id., page 13.

The examiner acknowledged that neither Rosen nor Tarkowski discloses packaging the TNF-specific reagents in a kit, but relied on Ahern to suggest that limitation: "Ahern teaches reagent kits offer scientists good return on investment. Ahern teaches kits save time and money because the kits already come[] prepared." Examiner's Answer, pages 11 and 13.

The examiner concluded that it would have been prima facie obvious to package the reagents taught by Rosen into a kit because Rosen "teaches mutations at -308 [of TNF- α] and aa13 and aa26 [of TNF- β] which are associated with predisposition to liver rejection." Id., page 12. Similarly, the examiner concluded that it would have been obvious to package Tarkowski's reagents in a kit because "Tarkowski specifically teaches two polymorphic genes which are associated with AD [Alzheimer's disease]." Id., page 13.

Appellant argues that the examiner's rejection should be reversed because, among other things, the cited references do not provide a sufficient suggestion or motivation to combine their teachings. See the Reply Brief, pages 13-15 and 17-19.

We agree with Appellant that the references relied on by the examiner do not support a prima facie case of obviousness. "[T]he Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art. '[The Examiner] can satisfy this burden only by showing some objective teaching in the prior

art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.” In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (citations omitted). “[T]he ‘motivation-suggestion-teaching’ test asks not merely what the references disclose, but whether a person of ordinary skill in the art, possessed with the understandings and knowledge reflected in the prior art, and motivated by the general problem facing the inventor, would have been led to make the combination recited in the claims.” In re Kahn, 441 F. 3d 977, 988, 78 USPQ2d 1329, 1337 (Fed. Cir. 2006).

In this case, the examiner has not adequately explained why a person of ordinary skill in the art would have been found it obvious to package the reagents taught by either Rosen or Tarkowski into a kit that would meet the limitations of instant claim 106. Rosen teaches a method of identifying organ donors having livers less likely to be reinfected by hepatitis C virus (HCV). See ¶ 0007. Rosen teaches that the TNF- α gene has a polymorphic position at -308: the allele TNF308.1 has a G at this position while the allele TNF308.2 has an A. See ¶ 0035. Rosen also teaches that “[k]nown TNF- β polymorphisms include the TNFc locus, the aa13 locus, the aa26 locus and the Ncol locus.” See ¶ 0028.

Rosen amplified and sequenced polymorphic positions in the TNF- α and TNF- β genes and found that livers from donors with the TNF308.2 allele in the TNF- α gene were reinfected by HCV more often and more severely than livers from donors with the TNF308.1 allele. See ¶ 0066. By contrast, “[t]here was no correlation between the TNF- β alleles and time to recurrence, severity of recurrence or the prevalence of rejection.” ¶ 0067.

Thus, Rosen teaches that a polymorphism in the TNF- α gene is informative in predicting which livers are more likely to be reinfected in HCV-infected patients, but that polymorphisms in the TNF- β gene are not. In view of Rosen's teaching that TNF- β -specific primers are useless for predicting likelihood of HCV reinfection, we conclude that the examiner has not adequately explained why Rosen would have led a person skilled in the art to package primers specific for both TNF- α and TNF- β into a kit.

Like Rosen, Tarkowski teaches PCR primers for amplifying parts of the TNF- α and TNF- β genes. See pages 2078-2079. Tarkowski analyzed the association between aspects of Alzheimer's disease (AD) and polymorphisms in the TNF- α and TNF- β genes, but concluded that "the levels of these cytokines did not differ significantly in patients displaying different alleles of the TNF gene." Abstract. See also page 2080, right-hand column, second full paragraph:

[T]he frequencies of TNF α 1 versus TNF α 2 alleles did not differ between patients with AD and control subjects, suggesting a lack of association between TNF polymorphism and the susceptibility for AD. The intrathecal TNF α levels or the degree of cognitive deficit did not differ significantly between the groups of AD patients with different TNF α or TNF β gene polymorphism, suggesting a lack of association between TNF polymorphism and the clinical severity of AD.

(Emphases added.)

Thus, Tarkowski teaches that the TNF- α and TNF- β polymorphisms that were examined were not associated with either the susceptibility to or the clinical severity of Alzheimer's disease in potential patients. In view of this teaching, we conclude that the examiner has not adequately explained why Tarkowski would have led a skilled worker to package the TNF- α - and TNF- β -specific primers disclosed by Tarkowski into a kit.

Other Issue

This application is said to be "a continuation-in-part of co-pending U.S. application serial number 09/613,887" (specification, page 1), which is the subject of appeal number 2006-1560. The claims in that application are directed to a method, rather than a kit, for perioperative screening. The examiner rejected the claims as obvious in view of, among other references, Pharmacogenetics⁶ and AAS.⁷

AAS discloses that different alleles of the BChE gene affect patients' reactions to succinylcholine (page 139, left-hand column), that "careful DNA analysis is really the only way to establish individual BChE genotypes" (page 140, right-hand column), that "[w]e have been able to sequence the entire BCHE coding region and consider all the possible structural mutations using PCR amplification" (*id.*), and that "anesthesiologists need to keep up to date about" the application of molecular biology tests to BChE variants (sentence bridging pages 140 and 141).

Pharmacogenetics discloses that cytochrome P4502D6 (CYP2D6) is involved in mediating drug biotransformation (page 309), including the transformation of codeine to its active form (page 317, left-hand column), and that by combining "rapid and specific PCR-based allele-specific amplification tests . . . [with] XbaI RFLP analysis, about 95 percent of all mutant alleles of CYP2D6 could be identified, allowing for the prediction of over 90 percent of PM [poor metabolizer] phenotypes" (page 314, right-hand column).

⁶ The reference is cited as "Pharmacogen[e]tics, Chapter 4, pp. 309-326" in the Information Disclosure Statement received in application 09/613,887 on April 6, 2001 (reference number 202 in the IDS).

⁷ La Du, "Butyrylcholinesterase variants and the new methods of molecular biology," Acta Anaesthesiologica Scandinavica, Vol. 39, pp. 139-141 (1995)

On return of this application, the examiner should consider whether the references cited in application 09/613,887, together with the prior art of record, would support a prima facie case of obviousness with respect to any of the claims in the instant application.

REVERSED

Lance Leonard Barry)
Administrative Patent Judge)

Donald E. Adams) BOARD OF PATENT
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